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The Honorable Tommy G. Thompson
Secretary of Health and Human Services
Washington, DC 20201

Dear Mr. Secretary:

The Clinical Laboratory Improvement Advisory Committee (CLIAC), the Department of Health and Human Services (HHS) Committee charged with advising you and HHS on matters related to the implementation of the Clinical Laboratory Improvement Amendments of 1988 (CLIA), is pleased to provide comments for consideration in the development of the final rule on the process and criteria for waiver determination. In the past two years, CLIAC has spent a significant amount of time considering the appropriate criteria and process for waiver and providing advice to the three agencies (Centers for Medicare & Medicaid Services, Centers for Disease Control and Prevention and Food and Drug Administration) responsible for implementation of the CLIA program. Our major concern is that waived tests are exempt from CLIA standards and oversight, and it is imperative to ensure the quality of this testing. At the CLIAC meeting on January 30, 2002, we developed the following recommendations and comments that we believe are necessary to ensure waived test quality and protect the health of the public.

<u>Home Use Approval</u>
As mandated in the CLIA statute as modified by the FDA Modernization Act of 1997 (FDAMA), waived tests are laboratory tests approved by the FDA for home use or simple tests that have an insignificant risk of an erroneous result. To be approved for home use, a manufacturer must demonstrate that a test is simple, and that a clinically meaningful signal (test result) can be generated by lay users. A threshold for accuracy is not required in the home use approval process; there is a risk/benefit analysis to determine the value of having the test available for patient self-testing. To be approved for waiver under the other provision in the CLIA statute, a test must be simple and have an insignificant risk of an erroneous result, and accuracy is used to demonstrate the low risk.

Because of the lack of uniformity in the criteria used in the two routes for waiver approval, there is a double standard in place and home use approval may be a “back door” for automatic waiver approval when tests can not meet other criteria (simple, accurate) for waiver. The CLIAC is very

concerned about this nonequivalence, and believes tests approved for home use should not automatically be waived under CLIA, because home use approval does not consider the expanded use of these products in clinical settings when the product is waived. We suggest technical corrections to the statutes be considered, where appropriate, to ensure that all waived products are simple and have an insignificant risk of an erroneous result. One of our principal concerns is that the clinical use of tests approved for home use is off-label use of these products, and there are serious implications when tests designed for self-testing are performed by health care providers on other individuals, especially in settings such as intensive care units or operating rooms of hospitals, as is currently the case. While we acknowledge the need for home use approval to ensure products are available for individuals to self-test, a higher level of accuracy is needed when this testing is performed in clinical settings.

Accuracy

As mentioned above, the CLIA statute, as modified in FDAMA, requires waived tests to be simple and accurate. We recommend accuracy be evaluated by comparing test performance to a measure of truth, and accuracy be determined using laboratory professionals in a laboratory setting. Measures of truth could include reference methods, designated comparative methods, well characterized reference materials or well characterized working methods. In certain circumstances and for specific tests, a measure of truth may also include clinical evidence of disease/health condition. For qualitative tests, accuracy assessments need to include an evaluation of clinical sensitivity, clinical specificity, and predictive values, and should consider prevalence of disease in a population.

The FDA 510(k) clearance process requires manufacturers to demonstrate substantial equivalence of a test to a device previously cleared by the FDA, which may include accuracy studies. However, to ensure accurate results for waived tests exempt from standards and not subject to regulatory oversight, it may be necessary to require a higher accuracy threshold than for moderate or high complexity tests, performed in laboratories required to meet standards for personnel, quality control and quality assurance. To meet this higher threshold for waiver approval, in some
cases, manufacturers may need to perform additional accuracy studies. If the accuracy studies used for the 510(k) clearance process meet the higher threshold for waiver, additional studies would not be necessary.

Precision Studies

CLIAC believes waived tests must be precise and demonstrate a low level of imprecision when testing is performed by intended users in intended use settings. We recommend precision studies include a representative sample of the intended user population in an intended use setting to provide a valid measure of test performance. In addition, we note that to document the untrained user ability to follow the package insert and perform the test correctly, the manufacturer must test the user's ability to understand quality control and test a patient sample.

Risk of Harm to Patients

One of the examples in the CLIA statute of the type of tests that could be waived are those which "pose no unreasonable risk of harm to the patient if performed incorrectly." However, it is impossible to objectively define the terms "unreasonable," "risk," and "harm", and all tests have some risk of patient harm if performed erroneously. In fact, a test that can't harm a patient if performed erroneously, can't help a patient if performed correctly. Data are needed on the impact of erroneous results of waived testing. In light of the fact that risk is difficult, or impossible, to measure, we stress the importance of considering the context of testing and clinical impact of waived tests, when making waiver decisions. It is also critical to consider all phases of testing (pre-analytic, analytic, and post-analytic) in assessing risk of harm and making waiver determinations.

Appropriate Tests for Waiver

We acknowledge the difficulty of attempting to establish regulations based on the context of testing. The same test may be used for screening, diagnosis, or monitoring, depending on the situation or patients being tested. Therefore, tests can not be automatically placed in one category, with the assumption they will always be used for that purpose, and regulated as such. When considering whether screening tests that require follow-up confirmatory tests should be waived, the CLIAC noted it would be useful to have more data on the frequency with which follow-up testing is performed when specified in test instructions. We do not believe the category of screening tests should automatically be excluded from waiver approval, but that each test should be individually evaluated.

Quality Control (QC) Testing

The CLIAC strongly supports the inclusion of QC testing requirements as part of manufacturer's instructions for waived tests, especially if QC testing is part of the fail-safe, or failure alert mechanism included in a waived test to ensure that no result is rendered when the test system malfunctions or is outside the reportable range for results. We strongly support requiring QC testing when it is used as a failure-alert mechanism. Manufacturers need to specify the required frequency and levels of QC in their claims to the FDA when applying for waiver, and lockout features should be required on test systems, when feasible, to ensure QC performance and accurate test results.

In several studies of waived laboratories, it has been noted that the laboratories are more likely to test QC, when it is included in test kits and described in manufacturer's instructions. However, QC performance can not be verified in waived laboratories, even if required, since these laboratories are not routinely inspected.

Labeling

Waived test instructions must be clear, easy to read, and understand, especially since waived testing personnel are often self taught, and there is a high personnel turnover rate in waived laboratories. It is useful to include step-by-step instructions separate from lengthy package insert materials, formatted as quick reference cards. We also recommend visual aids such as diagrams, charts, and drawings, or instructions provided on video's, CD's, or accessed via website. Education is key to ensuring quality waived test performance, as many personnel in waived laboratories do not understand the importance of following test instructions, including QC testing.

In an effort to assist laboratories in understanding the performance specifications of waived tests, the labeling should include performance data, and where relevant, sensitivity, specificity, and predictive values. For infectious disease tests, labeling should include prevalence data. If there are test limitations, or if testing is not appropriate for certain patients or populations, this information should also be specified in waived test labeling.

Surveillance/Post-approval Monitoring

We strongly support the concept of post-approval surveillance of waived tests. The implementation of such a program could provide useful information about the performance of waived tests in laboratories, and the CLIAC strongly supports monitoring test performance after products are waived. We urge HHS to make such surveillance mandatory when the waiver criteria and process are finalized through rulemaking. As part of the surveillance, we recommend re-evaluation of waived tests based on field performance 3-5 years after initial waiver determination, and development of a mechanism for withdrawal of waiver approval, if post-approval performance data shows substantive variance from the original waiver approval data.

General Recommendations

Although some of the CLIAC's concerns regarding waived tests apply to all testing, many of the concerns stem from the fact that waived tests are exempt from CLIA standards and oversight, and are performed by inexperienced testing personnel who may not have available or follow test instructions. These personnel do not always understand measures necessary to ensure the quality of test performance throughout all phases of testing, although they may wish to comply with requirements. Therefore, measures should be taken to ensure that personnel are knowledgeable regarding test performance, and understand the importance of following test instructions. One way of doing this may be to require a certificate of competence for testing personnel, after they have completed a course of instruction on a specific test system.

To offset the inexperience of testing personnel, it is imperative that the quality of waived tests be high. We recommend HHS be conservative in establishing waiver criteria, rather than establishing permissive criteria with the intent that they could be strengthened in the future. Waiver decisions must be based on science, and not opinion. Where possible, HHS should be flexible in the waiver approval process, to allow manufacturers, who believe certain criteria may not apply to their tests, to show why these criteria are not applicable.

In some cases, waiver is advocated as a means of increasing access to testing. Some individuals are concerned that not approving tests for waiver decreases access for physician office laboratories, especially in rural or underserved areas. However, others are concerned that increased numbers of waived tests and increased access to this testing will lead to increased numbers of personnel who do not understand or follow test instructions, and possible errors that could affect patient outcomes. Concerns about access to testing should not outweigh issues of maintaining waived test quality, especially since moderate complexity categorization is an option for access. Categorization of tests as moderate complexity ensures that minimal standards for personnel, quality control, and quality assurance are in place, without compromising access to testing. The CLIA standards were implemented to ensure quality laboratory testing regardless of testing site.

Thank you for this opportunity to provide comments on the development of the final waiver regulation. The CLIAC is available to provide clarification of these recommendations and remains committed to providing recommendations to ensure the waiver process is appropriate to exempt these tests from CLIA standards and assure quality testing for the nation's laboratories and the public.

Sincerely yours,

/S/ Toby Merlin, M.D.
Chairperson
Clinical Laboratory Improvement Advisory Committee